REMARKS

Claims 5, 7-9, 26-27, 29, 31, 37, 48-51, 56, 58, 69-70, 72, 74, 76, 78, 108, 110, 117, 127-129, 131-135, 137, 147, 150, and 156-167 were pending in the present application, prior to Amendment. Claims 56, 110, 135, 137, 147, 150 and 162-163 have been withdrawn from consideration, but Applicants note that, in accordance with MPEP 821.04(b), Applicants will be entitled to rejoinder of process claims that depend from and include all the limitations of an allowable product claim.

Applicants note that the Examiner did not enter the claims and response dated July 27, 2010, which Applicants filed in response to the Final Office Action of May 12, 2010. Accordingly, all amendments and claim identifiers provided herein are shown relative to the claims filed with the Supplemental Response dated October 13, 2009.

Applicants have canceled claims 27, 69, 74, 157, and 160 without prejudice. Applicants have amended claims 5 and 164 to address claim objections described below, amended claim 29 to depend from claim 26, and amended claims 166 and 167 to clarify the subject matter claimed. Applicants have also added new claims 168 and 169. Support for the amendments and new claims may be found in pending claims 5 and 164, and in paragraph [0321]. No new matter has been added.

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order in which they appear in the Office Action.

Claim Rejections – 35 U.S.C. § 112, second paragraph

Claims 27, 160, and 166 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite in the recitation of the phrase "unstructured peptide." Applicants respectfully traverse. The phrase is commonly used in the scientific literature to refer to peptides that have not folded into specific structures. In the specification, a linker that is an unstructured peptide is differentiated from a linker that includes one or more repeats of Ser_4Gly or $SerGly_4$, and a linker that is selected to provide steric geometry between a catalytic domain and a targeting moiety (for example, see

paragraph [0038]). Taken in light of the art-recognized use of the term and the teachings provided in the specification, the claim clearly sets forth the metes and bounds of the desired patent protection in a manner that is clear to one of skill in the art. However, solely to expedite prosecution, Applicants have canceled claims 27 and 160 and amended claim 166 to remove explicit reference to unstructured peptides. The foregoing are not made in acquiescence to the rejection and should not be understood to alter the scope of the pending claims. Applicants expressly reserve the right to prosecute claims using the same or similar language in future applications.

Claims 69 and 157 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite in the recitation of the phrase "resistant." The Examiner asserts that the term "resistant" is a term of degree, and it is allegedly unclear how much cleavage is required for the adzyme to be considered "resistant." Applicants respectfully traverse. The specification describes how autocatalysis disrupts the ability of the adzyme to act effectively on its target and provides examples of adzymes that decrease or prevent autoproteolysis (paragraphs [0407]-[0417]). In view of the detailed description provided in the specification and the level and understanding of one of skill in the art, Applicants submit that one of skill can readily appreciate the metes and bounds of the claimed invention. Nevertheless and solely to expedite prosecution, Applicants have canceled claims 69 and 157. Cancellation of these claims is not in acquiescence to the rejection and should not be understood to alter the scope of the pending claims. Applicants expressly reserve the right to prosecute claims using the same or similar language in future applications.

Claim 74 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite in the recitation of the phrase "adzyme inhibits biological activity of said substrate relative to..." The Examiner asserts the term is indefinite because there are allegedly many different biological activities a substrate can have which are independent from each other. Applicants respectfully traverse. The claim does not differentiate biological activities or select specific biological activities to inhibit. Rather, the claim recites "said adzyme inhibits a biological activity of said substrate relative to said biological activity in the absence of said enzyme" (emphasis added), which indicates that the same biological activity is considered in the presence or absence of an enzyme, regardless of the identity of biological activity. Nevertheless and solely to expedite prosecution, Applicants

have canceled claim 74. Cancellation of claim 74 is not in acquiescence to the rejection and should not be understood to alter the scope of the pending claims. Applicants expressly reserve the right to prosecute claims using the same or similar language in future applications.

Claim 167 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite in the recitation of the phrase "adzyme inhibits bioactivity of TNFα..." The Examiner alleges that the term is indefinite because TNFα can allegedly have several bioactivities such as activity of eliciting antibodies, inflammation, etc. Applicants traverse. The specification discloses numerous examples of TNFα activity, and describes pathological conditions associated with dysfunction of TNFα activity. One of skill in the art would readily recognize the activities encompassed by a claim reciting "bioactivity of TNFα." Nevertheless and solely to expedite prosecution, Applicants have amended claim 167 to point out inhibition of binding of TNFα to a TNFα receptor. Support for this amendment is found throughout the specification, for example in paragraph [0011]. Applicants' amendment to claim 167 is solely to expedite prosecution, is not in acquiescence of the rejection, and should not be understood to alter the scope of the pending claims. Applicants expressly reserve the right to prosecute claims using the same or similar language in future applications.

Applicants note with appreciation the comments in the Advisory Action of August 17, 2010 regarding claim 167. The Examiner states that the rejection of claim 167 would have been withdrawn, had the amendments been entered.

Claim Rejections – 35 U.S.C. § 102

Claims 5, 7-9, 37, 48-51, 58, 69-70, 72, 74, 76, 78, 108, 127-129, 156, 157, 158, and 164-165 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Holvoet *et al.* (JBC 1991, vol.266, pp 19717-19724, hereinafter "Holvoet"). The Examiner asserts that Holvoet teach a fusion protein of urokinase (a serine protease) fused with a fibrin-specific antibody. The antibody allegedly binds fibrin on a blood clot while the serine protease of the fusion moiety allegedly lyses the blood clot via cleaving fibrin polypeptide. As such, Holvoet allegedly anticipates pending independent claim 5 and all claims depending therefrom. The Examiner includes claim 164 in the rejection because the recitation of a single polypeptide in claim 164 is allegedly interpreted as "not a

complex of different proteins, and fibrin of Holvoet et al. is not a complex of different proteins" (page 6 of the Office Action).

Applicants traverse to the extent the rejections are maintained over the amended claims. Claims 69, 74, and 157 have been canceled without prejudice. Claims 5 and 164 and all claims depending therefrom have been amended to include a proviso that the polypeptide substrate is not fibrin. New claims 168 and 169 recite a proviso that the protease domain is not urokinase plasminogen activator. These amendments are believed to obviate the rejections under 102(b).

In the Advisory Action of August 17, 2010, the Examiner was allegedly "unable to find support in the specification or the claims as originally filed for a subgenus of polypeptides which exclude fibrin or a subgenus of protease domains which excludes urokinase plasminogen activator" (page 2 of the Advisory Action). Applicants point out that support for the proviso excluding fibrin may be found in the disclosure of fibrin as one of many potential substrates in Table 1, and in the disclosure of paragraph [0215] which states that "additional examples of cell surface associated or extracellular matrix targets for the subject adzymes include...fibrin..." Support for the proviso excluding urokinase plasminogen activator (also abbreviated uPA and called urokinase) may be found in paragraph [0321], which lists "certain preferred embodiments, [in which] proteases that are useful as catalytic moieties in the present invention are set forth." Applicants submit they may freely chose to omit species such as fibrin and/or uPA from the bounds of protection sought, since the species were originally disclosed in the specification. Under similar circumstances, the court held in *In re Johnson* that applicants could delete certain compounds from protection sought and claim less than the full scope of the disclosure. A "specification [which] supported the claims in the absence of the limitation...having described the whole, necessarily described the part remaining" (*In re Johnson*, 558 F. 2D 1008, 1019 (CCPA 1977). Thus, the instant specification necessarily describes the parts of the genus remaining after exclusion of fibrin and/or uPA, and Applicants assert that the specification supports the claimed genus of polypeptides.

Applicants maintain the arguments of record regarding why the claimed invention is novel in view of Holvoet. Applicants do not concede that the fusion protein of Holvoet meets all of the limitations of the claims because Applicants do not view Holvoet, or any other reference pointed to

by the Examiner, to support the conclusion that uPA (the protease domain in the Holvoet fusion protein) *itself* cleaves fibrin. Rather, the evidence appears to indicate that uPA (the protease domain in the Holvoet fusion protein) cleaves plasminogen to produce plasmin, and that plasmin (a protein which is **not** part of the Holvoet fusion protein) in turn cleaves fibrin.

Nevertheless, to expedite prosecution, Applicants have amended claims 5 and 164 to explicitly exclude certain elements present in Holvoet from the scope of the claimed invention. Accordingly, Holvoet fails to anticipate the claimed invention. Applicants' amendments are made solely to expedite prosecution, and are not in acquiescence to the rejection. Applicants expressly reserve the right to prosecute claims of similar or differing scope. Applicants respectfully request reconsideration and withdrawal of the rejection.

The Examiner further includes independent claims 158 and 165 in the rejection, because the fusion protein of Holvoet comprises a protease domain and allegedly "comprises the inherent ability to cleave peptide bond of substrate polypeptide of amyloid deposit or substrate polypeptide (claim 158) produce by pathogen or prethrombin (claim 165)" (page 6 of the Office Action). Applicants respectfully request clarification of these rejections. It is not clear how the fusion protein of Holvoet, an anti-fibrin antibody fused with the protease uPA (urokinase plasminogen activator), comprises these inherent abilities. Holvoet teaches that uPA targets plasminogen, a soluble zymogen in blood serum, and Holvoet is silent on the ability of uPA to cleave substrate polypeptides in amyloid deposits or polypeptides produced by pathogens. In fact, Holvoet does not teach or suggest that plasminogen is a component of amyloid deposits or polypeptides produced by pathogens, let alone a target for cleavage. Applicants remind the Office that "the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990). Similarly, Holvoet does not teach or suggest that plasminogen has the ability to cleave prethrombin, as the Examiner suggests, but Applicants wish to point out that prethrombin is not a substrate recited in claim 165, but is a protease domain. If the rejection of claim 165 is based on an alleged inherent ability of uPA to cleave prethrombin, then the rejection is misplaced. Applicants respectfully request clarification of

the rejection of claim 158, and request reconsideration and withdrawal of the apparently erroneous rejection of claim 165.

Claim Rejections – 35 U.S.C. § 103a

Claims 117, 165 and 167 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable in view of the combined teachings of Holvoet or Bhatia et al. (Intl. J. Cancer 2000, 85, 571-577, hereinafter "Bhatia") in view of Davis et al. (WO 00/64485, hereinafter "Davis"). The Examiner asserts that one of skill would be motivated to make the protein conjugate of Davis comprising chymotrypsin or matrix metalloproteinase (MMP), or elastase conjugated to an antibody by gene fusion methodology, as taught by Holvoet or Bhatia. Applicants traverse the rejections to the extent they are maintained over the claims, as amended. The cited references do not fulfill the requirements of a *prima facie* case of obviousness: (1) suggestion or motivation to combine the references, (2) reasonable expectation of success, and (3) consideration of all claim limitations (MPEP 2143). Claim 117 depends from independent claim 5 and, as discussed above, Holvoet does not teach the elements of claim 5. Neither Davis nor Bhatia remedy this deficiency. Davis discloses enzymes, including chymotrypsin or matrix metalloproteinase (MMP), joined by chemical conjugation to a targeting molecule which may be a chemical ligand or a protein. Bhatia discloses fusion proteins made up of a bacterial enzyme CPG2 and an antibody to the tumor-specific molecule carcinoembryonic antibody (CEA). Even if all of the elements of the pending claims were found in the references, which Applicants do not concede, there is no motivation to combine Holvoet, Davis and Bhatia. Starting from Holvoet or Bhatia, both the targets and the substrates were selected for specific purposes, either mediating fibrinolysis (Holvoet) or tumor-specific targeting of a bacterial enzyme (Bhatia). The exact components of these fusion proteins were selected and developed for the purposes indicated. Altering the ligands, enzymes, or methods of joining the proteins, as taught by Davis, would likely produce unsatisfactory results. For example, substituting chymotrypsin or MMP for uPA would be expected to eliminate the selective cleavage of the substrate plasminogen. Similarly, substituting chymotrpysin or MMP for CPG2 would destroy the ability of the fusion protein to convert a non-toxic pro-drug to a potent cytotoxic drug.

Applicants point out that "[i]f a proposed modification would render the prior art invention unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification." *In re Gordon*, 733 F. 2d 900, 221 USPQ 1125 (Fed. Cir. 1984). Accordingly, one of skill would not be motivated to modify Holvoet or Bhatia according to the teachings of Davis.

Conversely, starting from Davis, one would not be motivated to make the chemically-conjugated molecule of Davis as a fusion protein, as the Examiner suggests. Davis specifically teaches the benefits of using chemical conjugation, rather than using fusion proteins. Chemical coupling imparts greater flexibility in the design of the molecules, and further, facilitates the use of targeting domains that may be small organic molecules or other non-protein ligands. Davis enumerates many advantages of using non-protein targeting moieties on page 21, lines 1-12. In summary, Davis specifically teaches the advantages of using only chemical conjugation techniques, but does not lead one of skill to make fusion proteins. In fact, Davis teaches away from making fusion proteins because such fusions (i) would lack the benefits described by Davis for chemical conjugates and (ii) would be unsuitable for use in the context of non-protein targeting moieties. Applicants assert that there is no motivation to combine the fundamentally distinct teachings of Holvoet, Bhatia, and Davis to arrive at the claimed invention. Accordingly, Applicants respectfully request withdrawal of the rejection.

The Examiner reiterates rejections of claims 26, 27, 29, 31 and 159-161 under 35 U.S.C. § 103(a) as allegedly unpatentable over Holvoet in view of Guo et al. (Biotech and Bioeng, 2000, 70, 456-463; herein "Guo"). The Examiner asserts that one of skill is motivated to make a fusion protein (as taught by Holvoet) wherein an enzyme is conjugated to an antibody by a $(Gly_4Ser)_3$ linker as taught by Guo. Applicants traverse to the extent the rejection is maintained over the claims as amended. As described in detail above, Holvoet fails to teach or suggest each and every limitation of the claimed invention. Guo describes a fusion protein comprising L-asparaginase (ASNase), a $(Gly_4Ser)_3$ linker, and a protective scFv, but the disclosure of the linker and the use of a different antibody does not remedy the deficiencies of Holvoet. Accordingly, the combined

teachings of the cited references fail to undermine the patentability of the claimed invention for, at least, failing to teach or suggest each and every limitation of the claimed invention. Reconsideration and withdrawal of the rejection are requested.

Claim 51 remains rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Holvoet in view of Debburman *et al.* (PNAS 1997 94, 13938-13943, hereinafter "Deburrman"). The Examiner asserts that it would have been obvious for one of skill to make a fusion protein comprising a protease conjugated to a specific antibody as taught by Holvoet, in order to target prion proteins as taught by Debburman. Applicants traverse the rejection to the extent it is maintained over the claims as amended. As described in detail above, Holvoet fails to teach or suggest each and every limitation of claim 51, which depends from claim 5. Deburrman does not remedy the deficiencies of Holvoet. Accordingly, the combined teachings of the cited references fail to undermine the patentability of the claimed invention for, at least, failing to teach or suggest each and every limitation of the claimed invention. Reconsideration and withdrawal of the rejection are requested.

Claims 131-134 remain rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Holvoet in view of Sanderson et al. (Medic. Res Rev 1999, 19, 179-197, hereinafter "Sanderson"). The Examiner asserts that one of skill would be motivated to add a reversible protein inhibitor as taught by Sanderson in order to make a pharmaceutical preparation comprising a fusion protein as taught by Holvoet. Applicants traverse the rejection to the extent it is maintained over the claims, as amended. As described in detail above, Holvoet fails to teach or suggest each and every limitation of claims 131-134, which depend indirectly from claim 5. The features provided by Sanderson fail to remedy the deficiencies of Holvoet. Accordingly, the combined teachings of the cited references fail to undermine the patentability of the claimed invention for, at least, failing to teach or suggest each and every limitation of the claimed invention. Reconsideration and withdrawal of the rejection and requested.

In conclusion, Applicants contend that the claims are nonobvious in view of the cited references. Accordingly reconsideration and withdrawal of the rejections under 35 U.S.C. § 103(a) are requested.

Double Patenting

Claims 5, 7-9, 26-27, 29, 31, 35, 37, 52-53, 58, 69-70, 72, 74, 76, 78, 108, 119, 127-129, and 131-134 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1, 4-5, 30-34, and 37-41 of copending Application Nos. 10/792,498 and 10/650,591.

Applicants have canceled claims 27, 69, 74, 157, 160 without prejudice. With regard to the remaining claims, Applicants reiterate that if conflicting claims are first allowed in these two co-pending U.S. Applications, Applicants note that, pursuant to 37 C.F.R. § 1.130(b), a timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(c) may be used to overcome the double patenting rejection. In the meantime, and given that there has been no indication of allowable subject matter in the instant application, Applicants ask that this rejection be held in abeyance until indication of allowable subject matter. Applicants will submit a terminal disclaimer, if necessary, upon indication of allowable subject matter.

Applicants note that, in accordance with MPEP 804.I.B., the Examiner will maintain the provisional double patenting rejection until there are either no longer any conflicting claims or the double patenting rejection is the only remaining rejection in at least one of the applications.

Co-Pending Applications

The following co-pending, commonly assigned applications are brought to the Examiner's attention: application serial number 10/792,498 and 10/650,591. The Examiner is obviously aware of the existence of these applications as they are used in the above outlined double patenting rejection. The Examiner is invited to consider all past, present, and future prosecution in these co-pending applications.

CONCLUSION

For the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the pending rejections. Applicants believe that the claims are now in condition for allowance and early notification to this effect is earnestly solicited. Any questions arising from this submission may be directed to the undersigned at (617) 951-7000

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 18-1945, under Order No. COTH-P01-001 from which the undersigned is authorized to draw.

Dated: September 13, 2010

Respectfully submitted,

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